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Keywords
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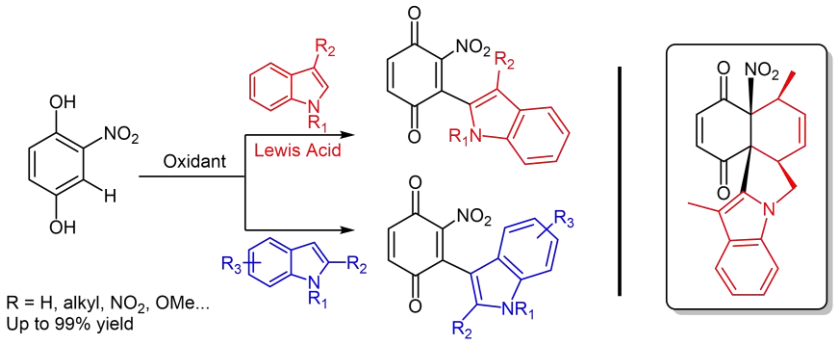

An Entry to Indole Quinones Using in situ Generated Nitrobenzoquinone

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ABSTRACT

A direct synthesis of polycyclic indoles from nitrohydroquinone and indoles is reported. Pentacyclic adducts can be obtained by a tandem conjugate addition/Diels-Alder strategy.

New methods for the synthesis of natural or synthetic molecules bearing the indole subunit continue to be reported.[1] In part this is due to the abundance of indole containing natural products.[2] Since aryl indoles and carbazoles are recognized as privileged structures, studies on synthetic analogs have been an active area in medicinal chemistry.[3] Representative compounds include the indole analog of morphinan (**1**) and the synthetic quinone (**2**) in Figure 1.[4] Previous uses of nitroquinones in organic synthesis include the innovative synthesis of indolequinone by Parker and Sworin[5] and the synthesis of euryfurylquinone by Valderrama and coworkers[6].

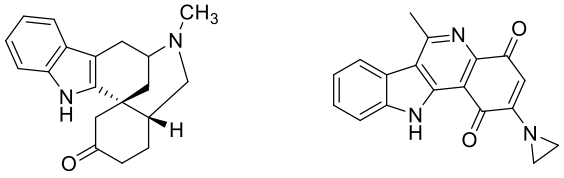
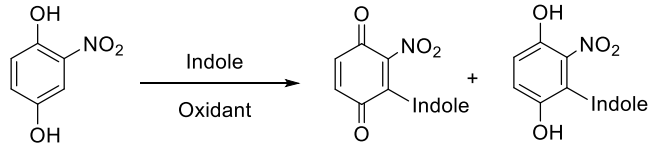


Figure 1. Bioactive indole natural products

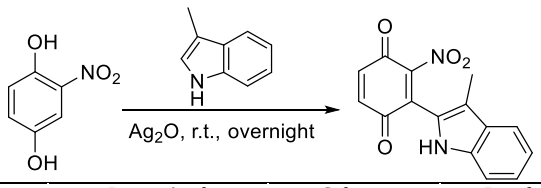
Our approach to the synthesis of indole containing quinones began with nitrohydroquinone (**3**), which was readily available from demethylation of 2,5-dimethoxynitrobenzene.[7] The corresponding quinone is unstable to storage, but it can be generated in situ using an oxidant such as silver oxide or MnO_2 and readily reacted with nucleophiles.[8] To the best of our knowledge this is the first report of the reaction of nitrobenzoquinone with indoles. As illustrated in Scheme 1, the product can be a hydroquinone or a quinone depending on the amount of oxidant employed. Hydroquinones can be converted to substituted quinones by excess oxidant (2.0 equiv).



Scheme 1. Reaction of **3** with indoles

The reaction of **3** with 3-methylindole was examined in several solvents and with several Lewis acids. The results of our experiments are collated in Table 1. Unfortunately, bismuth nitrate and copper acetate did not give promising results. Solvent screening showed that **4a** was able to obtained from dichloroethane in low yield. The best yield was obtained using silver (I) oxide and cerium (III) chloride in dichloroethane at ambient temperature for 3 hours. The use of cerium chloride was prompted by our previous study that Lewis acid was able to promote conjugate additions to quinone-type molecules.[9]

Table 1. Screening for Lewis Acids and Solvents (3-methylindole)



Entry	Lewis Acid	Solvent	Result
1	-	$CHCl_3$	0%
2	$Bi(NO_3)_3$	DCM	Trace
3	$CeCl_3$	DCM	35%
4	$Cu(OAc)_2$	DCM	0%
5	$Bi(NO_3)_3$	MeOH	0%
6	$CeCl_3$	$CHCl_3$	0%
7	**$CeCl_3$**	**DCE**	**49%**
8	-	DCE	28%
9	$CeCl_3$	THF	<5%
10	$CeCl_3$	Acetone	0%[a]

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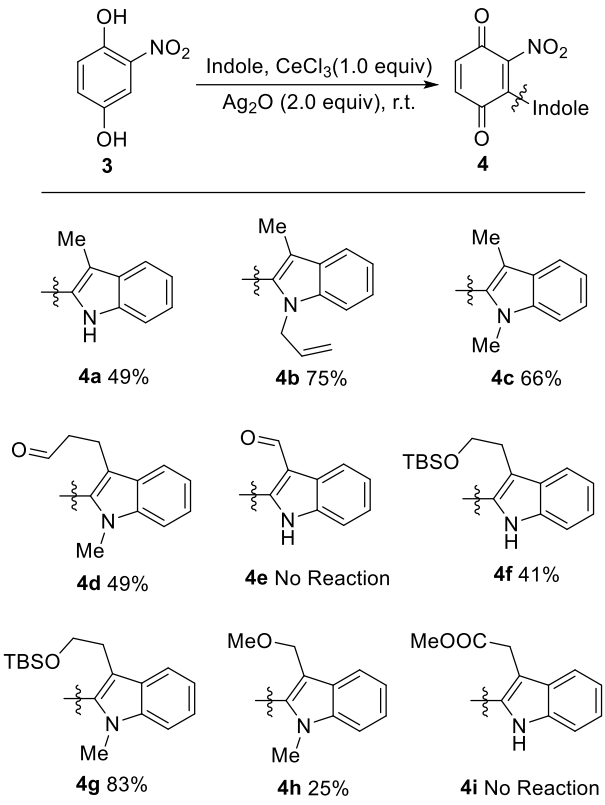
11	$CeCl_3$	DMSO	0%

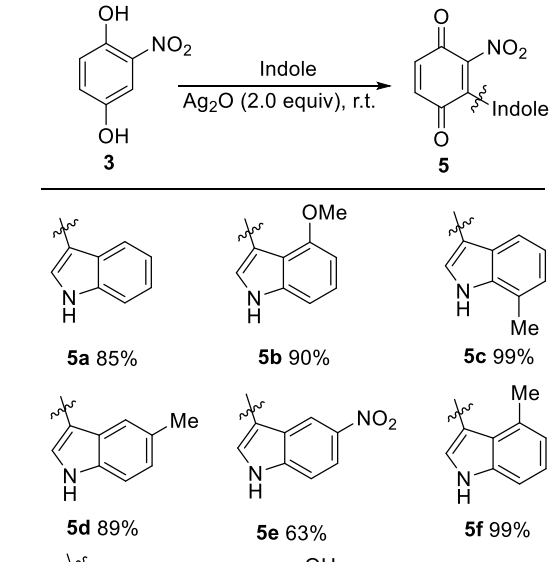
[a] No Reaction Observed

We next evaluated the reactions of 3-substituted indoles with **3** using the reaction conditions worked out with 3-methylindole. As shown in Scheme 2, methyl or allyl substitution on the indole nitrogen does not inhibit the reaction (**4b**, **4c**, **4g**). The presence of an electron-withdrawing substituent at C-3 prevents the reaction (**4e**, **4i**). However, a carbonyl group remote from the indole does not inhibit the reaction as shown with product **4d**.



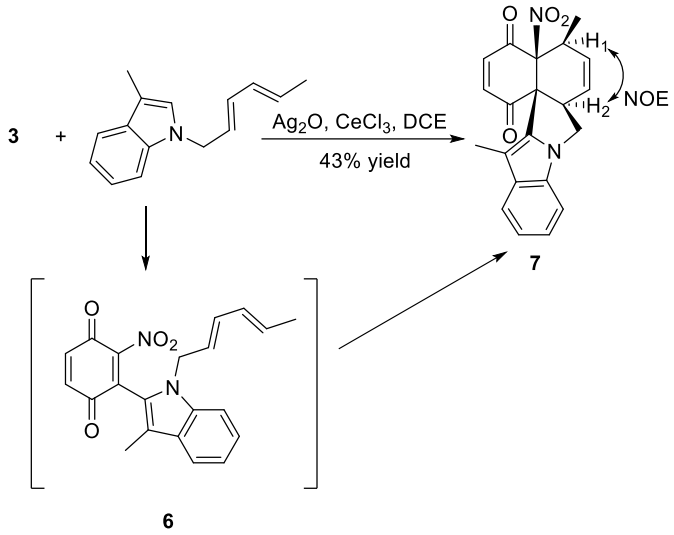
Scheme 2. Adducts of **3** with 3-substituted indoles

Indoles without a substituent at C-3 react readily without Lewis acid. As shown in Scheme 3, substitution at the 2-position does not hinder the reaction (**5i**). Substitution of electron donating groups on indoles gave generally good yields. The electron withdrawing effect of the NO_2 group on the indole ring lowered the yield (**5e**). Although a variety of substituents can be presented on the six-membered ring, the reaction does not occur with a phenol substituent (**5h**).



Scheme 3. Adducts substituted at C-3 of indole

As depicted in Scheme 4, more complex structures can be generated if a diene is connected to the indole nitrogen atom. Compound **6**, readily available from 3-methylindole and 1-bromo-2,4-hexadiene, reacts with **3** to produce the pentacyclic adduct **7**, the result of a tandem conjugate addition to nitrobenzoquinone followed by an intramolecular Diels-Alder reaction. The cis relationship of H_1 and H_2 was assigned by ^1H NOE experiment. The cis ring junction was proposed based on Marchand's study on the Diels-Alder reaction between nitroquinone and cyclopentadiene, where the nitro group functions as the directing group. [11]



Scheme 4. Tandem conjugate addition/Diels-Alder reaction

In conclusion, we had developed a method for generating indole substituted quinones via a tandem in situ oxidation – conjugate addition – oxidation mechanism. Both 2-H and 3-H indoles proceed in good to excellent yields.

Acknowledgments

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References and notes

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12. **General Experimental Procedure**, nucleophilic addition of 3-alkyl indoles to nitroquinone: (**4a**). To a 5 mL round bottom flask charged with solid **3** (47 mg, 0.3 mmol, 1.0 equiv), Ag_2O (139 mg, 0.6 mmol, 2.0 equiv) and $CeCl_3$ anhydrous (74 mg, 0.3 mmol, 1.0 equiv), dichloroethane 3 mL was added followed by fast addition of 3-methylindole (43 mg, 0.33 mmol, 1.1 equiv). The reaction mixture was stirred at r.t. covered by aluminum foil for 3 hours, and filtered through a silica pad. Solvent was removed under vacuum and the crude was loaded on column. Purification by flash column chromatography (ethyl acetate: hexane 1:2) gave the pure product as a brown solid (42 mg, 49% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ = 10.12 (s, 1H), 7.61 (d, J=8.0, 1H), 7.47 (d, J=8.2, 1H), 7.25 (ddd, J=8.2, 6.9, 1.1, 1H), 7.16 – 7.06 (m, 3H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, Acetone-d_6) δ = 185.99, 178.19, 139.32, 138.28, 135.90, 130.21, 129.40, 125.49, 122.02, 120.71, 120.60, 118.84, 112.73, 10.30; HRMS (ESI-QTOF) calcd for $C_{15}H_{10}N_2O_4$ $[M + H]^+$ 283.0713, found 283.0707.
13. Nucleophilic addition of 3-H indoles to nitroquinone (**5a**). To a 4 mL glass vial, **3** (15.6 mg, 0.1 mmol) and Ag_2O (46.4 mg, 0.2 mmol) were mixed as a suspension in DCE (0.5 mL) at r.t. Indole (14 mg, 0.12 mmol) was added fast as a solid, and then the reaction mixture was vigorously stirred overnight covered by aluminum foil. After the reaction was finished (monitored by TLC), the mixture was filtered through a short silica pad, and flushed by ethyl acetate 3 times. The solution was concentrated under vacuum and dry loaded on a silica column. The crude product was purified by flash column chromatography (ethyl acetate: hexane 1:2) gave **5a** as a dark purple solid (23 mg, 85% yield). ^{1}H NMR (400 MHz, Acetone-d_6) δ = 11.24 (s, 1H), 7.72 (s, 1H), 7.54 (dt, J=8.1, 1.0, 1H), 7.46 (dt, J=8.1, 1.0, 1H), 7.23 (ddd, J=8.2, 7.1, 1.2, 1H), 7.17 – 7.10 (m, 2H), 7.06 (d, J=10.2, 1H); ^{13}C NMR (101 MHz, Acetone-d_6) δ = 186.50, 178.51, 138.54, 137.85, 135.72, 132.68, 132.32, 127.02, 124.08, 122.06, 121.37, 113.27, 105.01; HRMS (ESI-QTOF) calcd for $C_{14}H_8N_2O_4$ $[M + H]^+$ 269.0054, found 269.0057.